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GROWTH IN LIVING AND NON-LIVING SYSTEMS

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GROWTH has perhaps a better claim than any other life-process to be called "fundamental," since it is the indispensable basis or condition of all vitality. This is true not merely in the obvious sense that all organisms are products of growth; even when an animal or plant has ceased to "grow," *i. e.*, add to its total living or organized material, it continues automatically to renew its own substance and to repair losses and damage; without this continual renewal no life can persist. We may thus regard the adult organism as still "growing," but the growth is "latent" —masked by the simultaneous loss inseparable from all vital activity. Visible increase in size is thus not the only evidence of growth; whether an organism grows visibly or not is in fact determined by the relative rates of two opposed processes, one of which builds up and accumulates, while the other breaks down and dissipates. In all life the primary or fundamental process is the building-up of the specifically organized living substance by constructive metabolism; but this process is always accompanied by chemical breakdown or destructive metabolism, with loss of material to the surroundings. Briefly, therefore, we may describe the essential situation as follows: when metabolic construction exceeds destruction there is "growth" (in the ordinary sense of visible increase); when the two are equal there is balance, or simple maintenance; when destruction predominates there is regression or atrophy. Visible growth represents simply the accumulated excess of construction over destruction.

This constant association of destruction and repair has long been recognized as the essential or distinguishing peculiarity of the living state; while the organism "lives," the effects of loss or destruction are continually being offset or compensated (often over-compensated) by new construction. The life process is thus

fundamentally a process of construction; it is a synthetic or creative agency; and all of its special peculiarities as a natural process are expressions of this characteristic power of specific synthesis. Claude Bernard has given perhaps the clearest and most comprehensive expression of this fundamental fact, which was already perceived by Lavoisier and in a vague way appreciated even in ancient times (*cf.* Heracleitus). The following passage is characteristic:[1]

> The synthetic act by which the organism maintains itself is at bottom of the same nature as that by which it repairs itself when it has undergone mutilation, or again by which it multiplies and reproduces itself. Organic synthesis, generation, regeneration, reintegration, healing of wounds (cicatrization) are different aspects of an identical phenomenon. . . .

Bernard's characterization is well known; "la vie, c'est la création;" he thus emphasizes the all-importance of construction or synthesis in the vital process.

Living material, then, is primarily *growing* material. In higher organisms this is sufficiently obvious in early development; later it becomes less and less evident because of the progressive increase of the destructive processes—relatively to the constructive—in the total metabolism. It is clear, however, that without the continuance of the synthetic processes which determine growth there can be no continued life at any stage. Growth therefore must be regarded as the universal index of the presence of life. We recognize this in the case of lower organisms like bacteria; and test their "livingness" by determining if they are capable of growth; if there is no proliferation in the culture medium the culture is a sterile one; either no organism were introduced, or those introduced were "dead."

Most multicellular animals and plants reach their final or adult stages through a process of progressively increasing size and complexity, beginning usually with a small and structurally simple germ (*e. g.* egg-cell); we describe this germ as "developing into" or "growing into" the adult form. This verbal usage expresses incidentally the necessary dependance of reproduction on growth. The growth involved in a single reproduction is often very extensive; thus the ratio between the mass of an adult human being and that of the fertilized egg-cell from which he develops is approximately fifteen billion to one;[2] this enormous accumulation of material occurs in each reproduction. There may, however, be reproduction without simultaneous growth (certain cases of fission) as

[1] Leçons sur les phénomènes de la vie, Vol. 2, p. 517.

[2] *I. e.*, the ratio of the mass of an individual of 60 kilo to the mass of an ovum of 200μ diameter (volume about .000004 c.c.).

well as growth without reproduction, and it is important to realize clearly the general nature of the organic processes which these terms represent. This may best be done by considering the case of micro-organisms; here the two processes are less sharply distinguishable and the terms are often used synonymously; thus bacterial growth and bacterial reproduction are usually regarded as identical. In such cases, reproduction simply follows automatically and regularly upon growth, so that the two are not practically separable; the one involves the other. Reproduction has been defined as "discontinuous growth," and this phrase expresses a conception which seems to be universally applicable. The essential fact in every case of reproduction is that portions of the growing organism continue to grow after detachment from the parental stock, and in so doing give rise to other complete organisms of the same kind. Reproduction of higher plants by cuttings is a case in point and in animals asexual reproduction and regeneration of the whole from a fragment afford similar instances. From such cases the logical transition to cases of gametic reproduction is simple; in this case the detached portion is a specialized unicellular structure (egg-cell) requiring fertilization in order to start its cycle of growth; but it represents none the less a detached portion of the parental organism.

What we observe in the case of higher animals is that when we trace the organic individual back to its beginning—or at least to the stage usually regarded as the beginning of individual life—we come finally to a small often microscopic mass of protoplasm, usually a single cell (germ-cell) which itself is the product of growth from the parent organism. In this germ we see little or nothing of the characteristic organization of the adult. Yet it is by the progressive accumulation and transformation—through the activity of this at first minute portion of living substance—of materials taken from the surroundings that the adult organism is by degrees built up.

Let us now consider briefly, from the point of view of general physiology, the essential nature of this process of growth or upbuilding, which we call individual development or ontogeny.

The germ adds to its substance, or *grows*, by incorporation of non-living materials taken either from the surroundings or from its own reserves (yolk),—food, water, salts; these it transforms physically and chemically in a definite manner which is specific for each organism. The most remarkable chemical feature of this transformation is the predominance of certain complex syntheses, especially the synthesis of colloidal substances of high molecular weight and highly specific or individualized chemical constitution.

These are the proteins, which are regarded by most biologists as forming the basis of organic specificity. Part of these substances, together with certain other products of the metabolic transformation, are chemically stable under the conditions prevailing in the living system, and are laid down in definite situations and at definite times in the form of a more or less solid, resistant or permanent residuum or deposit which forms the structural substratum of the growing organism. And since the rate of these synthetic or constructive processes exceeds that of the accompanying destructive processes, especially in the early stages of development, the living and organized material steadily accumulates; in other words, the organism grows. The rate of growth is not uniform in different regions; usually certain regions proliferate actively at certain times; then, as their growth activity subsides, other regions become active; the existence of growing zones or growing apices (buds or shoots in plants) is in fact one of the most characteristic features of developing organisms. All of this growth proceeds in an orderly and definite manner, in regular sequence and with strict correlation between the rates of growth in the different regions. Eventually the whole system acquires a more or less permanent form and dimensions, corresponding to the adult state; after this stage is reached the constructive processes gradually become less and less active, and eventually they fail to offset the destructive processes. Natural death then follows.

As the germ or embryo grows it "differentiates," *i. e.*, becomes by degrees more and more diversified, structurally, chemically, and physiologically. Different regions are set apart as the seat of special formative processes which give rise to special morphological structure with corresponding special physiological activity, and by degrees the systems of organs so clearly distinguishable in the adult make their appearance. The development of correlating or integrative mechanisms goes hand in hand with this differentiation. It is customary to regard differentiation as a process distinct from growth, since its essential feature is the appearance of new qualitative characters, both structural and functional, *i. e.*, of diversification; while the term growth has a primarily quantitative significance and has reference to increase in size, considered as such. Differentiation in embryonic development is perhaps the most impressive and mysterious of all organic processes, and its apparently purposive character has long furnished the vitalists with their strongest arguments. In the multicellular organisms it appears to have acquired a special physiological basis or determinative mechanism which has become superposed on that of simple growth—as we find it in unicellular organisms where cells give

rise typically only to other cells of the same kind. Apparently some additional factors, which impart definite and special directions to the formative processes in different cell-groups, are present in the higher organisms; and the evidence from genetic and cytological studies indicates that this special basis for differentiation is to be found in the specific differences between the chromosomes of the germ-cells. In some way, depending apparently on the manner in which the elementary chemical components of these structures are sorted or distributed in the series of mitotic cell-divisions, special kinds of structure-forming metabolism are localized in definite regions of the developing embryo.

The "chromosome theory of heredity" has performed notable services and is probably true, even if it is not the whole truth. But it should not be overlooked that growth and heredity, in their most general aspects, must be independent of special mechanisms of this kind. Specific growth and its manifestation in heredity are the final or visible expressions of the property of specific metabolic construction, which is based on specific chemical synthesis and is possessed by all forms of living matter—we may even say by all living structures which preserve their identity during the life of the cell or organism of which they form part. The chromosomes themselves grow and reproduce, and this capacity can hardly be referred to the existence of sub-chromosomes; in this respect chromosomes are like all other living structures. This, however, need not prevent their having a special function as repositories and distributors of substances which control the special nature of the structure-forming metabolism in different parts of the organism.

While in higher organisms growth and differentiation, considered abstractly, may be regarded as two distinct processes, in reality the two are inseparable, and on a strictly objective view these terms must be regarded as denoting two aspects of a single complex process rather than two essentially different processes. "Growth" is usually given a quantitative definition, as signifying increase in the quantity or mass of the living material; thus we may express the growth of an embryo in mass-units or weights and draw curves showing correctly, within certain ascertainable limits of error, the rate of growth from day to day. But while this growth is proceeding it is in fact associated with increase of complexity, with the continual appearance of new qualities and activities in the organism. These features of the total organic process differ from growth in not being representable in simple quantitative terms and in requiring special methods of description; yet they are all *based* upon growth. Such considerations illustrate the sense in which the growth-process is fundamental or

foundational in all life-processes. Obviously without its occurrence the adult organism could never arise from the minute "undifferentiated" egg-cell. Whatever the special nature of the formative activities may be, it is at least clear that they must have material to work on, and this material is furnished by growth.

Increase in the quantity of organized or living material is simple growth, and proceeds automatically in all forms of protoplasm under favorable conditions. Increase in structural or organizational complexity is usual when growth is associated with *development*—as in higher organisms—but is not always present; thus we do not usually conceive of development as occurring in dividing bacteria or yeast cells. In the lowest organisms the result of growth is the formation of more and more living material of the same kind, simple and "undifferentiated," structurally and physiologically. For example, there is no progressive increase of complexity during the growth of bacteria in a culture medium—except in so far as this is necessarily involved in any quantitative increase; more and more protoplasm of the same kind, definite and specific in structure and activity, is built up from the environmental materials by a strictly repetitive kind of process. We may note here, as a matter of general or philosophical interest, that it is simply because the same series of transformations is repeated in each bacterium as it grows and divides that we conceive of the process of reproduction as involving "heredity." The daughter-cell repeats the life-cycle and hence the qualities and activities of the parent-cell. If we wish, we may express this fact by saying that it "inherits" its qualities from its parent; but this terminology need not confuse our conceptions of what really and objectively occurs. In higher organisms we have the same type of situation, except that a more complex cycle of metabolic and formative transformation is repeated in each reproduction. In either case the *constancy* of the metabolic syntheses which underlie the growth-processes forming the new living material is what makes possible the constancy of the outcome in the growth and development of the individual organism, whether this organism be a bacterium or a human being.

In many animals evidence of differentiation is seen early in development, *i. e.*, before the germ has proceeded far in its growth. Even uncleaved eggs show partial differentiation in many cases. In the vertebrate embryo the various systems of organs, nervous, skeletal, digestive, circulatory, are distinguishable soon after the germ layers are formed; these embryonic foundations, once established and partly individualized, continue to grow and soon exhibit secondary differentiations; their functional activity and interdependence increase at the same time. Each organ system is

often described as if it developed independently by inherent potencies of its own; but this is merely an accident of descriptive procedure, where the whole is often disregarded in considering the details. In reality no organ system or other part develops in isolation. The growth and development of the organism as a whole is marvellously balanced and correlated; a system of checks and controls prevents the excessive growth of one region at the expense of another. The shape and proportions of the embryo at each stage of development are as constant as they are in the adult; and a similar constancy must characterize the underlying physiological processes. The problem of the physiological conditions determining the correlation of growth processes in organisms has many aspects of fundamental interest. It includes the special problem of the nature of transmissive processes in protoplasm (nervous and related transmissions), as well as the broader biological problem of the unification or integration of the various organic processes of the individual. The unity of the formative processes represents a special feature of organic unity in general, and cannot be considered apart from other cases of functional integration. Development is perhaps the most striking example of an organic activity which is at the same time highly complex and highly integrated.

The final or adult stage of even the highest animals is attained with a constancy and exactitude which never fail to arouse our wonder. We cannot trace the causal sequence in any detail and may never be able to do so. And yet when we consider the matter more closely, and especially when we observe the degree to which exactitude—constancy of repetition—is inherent in all natural processes (as the achievements of physics and astronomy show perhaps most clearly), it ceases to be a matter of special surprise that organic processes like growth and development should exhibit a similar regularity. If, as physiology assumes, the organism is a synthesis of simpler physical and chemical processes, its activities should partake of the regularity of the component processes. In fact, a similar quantitative regularity becomes apparent whenever single organic activities are isolated and presented to observation in a form suitable for measurement. Accordingly, with constancy of initial constitution and constancy of environing conditions we should expect a living germ, like any other natural growing system, to exhibit constancy in its cycle of development. That it does show such constancy is the very fact which we designate as "heredity." Many years ago Professor C. O. Whitman gave clear and striking expression to this thought in the following words: "Germ-cells behave alike in development, not because anything is transmitted to them, but because they represent identical material and

constitution and are exposed to essentially like environmental conditions.'' And with respect to the exactitude of development he says: ''We easily forget that only physical processes can approach such exactness.''[3] We may safely assume that given a germ of a definite constitution and normal environmental conditions, a ''spiritus rector'' is as little needed to guide development along a constant course to a definite or predetermined end as to guide the course of the planets about the sun. Constancy in the initial constitution of the germ, and in the environmental conditions implies constancy in the sequence of physical and chemical transformations which form the basis of growth and development.

Although the developing organism is a highly unified or integrated system, yet many facts, especially those of tissue culture and certain departments of experimental embryology, show that the cells forming each system of organs have an independent power of growth; when they are isolated in sterile plasma and supplied with oxygen they will continue to proliferate and give rise to other cells of the same kind. An isolated part of an embryo will undergo differentiation; or if it is transferred from its normal position in the embryo to a distant region in the same or another embryo (as in grafting experiments) it will continue, for a time at least, with its usual development and differentiation. Such facts illustrate again the specific nature of the formative processes or powers of growth innate in each form of protoplasm; when it grows it gives rise to other protoplasm of the same kind, similarly constituted structurally and with a similar chemical organization and similar physiological activities. We have evidence, in the existence of specific cytolysins, of the chemical differentiation of the different tissue-proteins of the same animal, just as we have evidence of specific chemical differences between the corresponding proteins of different animals. While our most delicate means of discriminating between different native proteins are the biological tests, especially those of anaphylaxis and precipitin-formation, which do not give us direct information of chemical constitution, yet we cannot doubt that the structural proteins of each species of cell have specific or highly individualized peculiarities of composition and configuration; and that these peculiarities are related in a definite manner to the specific structural and physiological peculiarities of the cell. Reichert has shown that the hæmoglobins from different animals have specific crystallographic peculiarities; *i. e.*, in separating from solution they form aggregates of specific form and structure. No doubt the same process occurs in the case of

3 See Vol. 2, pp. 179, 180, of Whitman's posthumous Studies on Inheritance in Pigeons (Carnegie Institution, 1918, edited by O. Riddle).

the other cell-proteins as they are deposited during growth to form the protoplasmic structures characteristic of the species; if this is the case, the specific morphological or histological features of a given cell must depend ultimately upon the specific features of chemical structure and configuration possessed by the cell-proteins. The toxic effects of foreign proteins upon cell-structure, as seen (*e. g.*) in specific hæmolytic effects, are an indication of the incompatibility of such compounds with the normal cell-structure of the species.

In all cases the cell-proteins, like the majority of cell-constituents other than salts and water, are synthesized within the cell by the processes of specific constructive metabolism from materials furnished by the surroundings. Since in general every chemical compound, when it is deposited in solid form from a solution, forms a definite type of structure, seen in constancy of crystal form, it is to be expected that in living protoplasm the formation and deposition of chemical compounds with specific chemical characters will involve the origination of specific structure, and secondarily of specific physiological activities corresponding to that structure.

In general any solid material with a specific chemical composition must possess a specific physical structure. This conclusion is not merely a generalized inference from the facts of crystal-formation, special texture or other properties of solids, but has been brilliantly substantiated by the methods of X-ray analysis of crystal structure recently developed in England by W. H. and W. L. Bragg. And we may infer that the special features of the new structure formed in any growing system, whether living or non-living, will have a similar dependence on the chemical composition of the structural material.

The study of the structure and properties of growing inorganic systems, especially as related to the chemical composition of their components, may thus be expected to throw some light upon the more general features of the growth-process in organisms. Such systems may be regarded as elementary or generalized models of organic growth. Organic growth is peculiar in the complexity of its materials, conditions and outcome; it gives rise to the highest products of synthesis found in nature; but in other respects it shows various definite affinities with certain types of inorganic growth. It may be of interest, therefore, to consider briefly some results of a study which I have recently made of certain inorganic growth-models, and their bearing on some of the more general problems of organic growth.[4] In particular the conditions determining the structural specificity of these inorganic growths, and

[4] *Biological Bulletin*, 1917, Vol. 33, p. 135, and 1919, Vol. 36, p. 225.

the manner in which they are influenced by external conditions (electricity, contact, temperature, presence of foreign chemical substances), show certain resemblances to organic growth which seem to throw light on some of the more fundamental features and conditions of the latter.

It is well to realize that growth processes are by no means confined to living organisms, but are to be found everywhere in nature—in other words that organic growth is a special example of a universally distributed type of natural process. Hence the analysis of what growth is, in its more general and simpler aspects, must be a matter of great interest to all biologists. The more special problem of the nature and conditions of organic growth, as distinguished from other forms of growth, is likely to become more open to successful attack if the simpler cases are considered first.

By the term growth, as applied to ordinary physical objects, we usually mean simple increase in the quantity of some material forming a more or less definite system or aggregate; the system thus increases in size while retaining its special distinguishing properties or identity. Simple accretional growth are instances, *e. g.*, avalanches, stalactites, deltas, crystals. In the case of organic growth something additional and highly characteristic is involved. Growth is not the result of simple accumulation of materials already existing as such in the environment of the growing system; but the added material is chiefly of a kind not found in non-living nature and formed within the system itself through the specific chemical transformation of material taken from the surroundings. New chemical compounds are created in new and characteristic structural and other relationships. Part of the material thus synthesized, especially the protein and lipoid part, is built up to form the living and organized substratum of the growing cell or organism.

Such considerations show (incidentally) that the conception of organic development prevailing at one time, of an unfolding, increasing, or becoming evident of something already in existence or latent in the germ, is no longer a tenable one. The creation or new appearance of *novelty* seems to be an essential fact in most if not all natural occurrence; and this is notably the case in organic growth. To a modern biologist the epigenetic conception of development is the only one possible; new characters arise at each ontogenetic stage in correlation with the formation of new chemical compounds in new physical combinations.

In the case of inorganic growth, therefore, we should expect to find the closest resemblances to organic growth in those growing

systems where growth is dependent on the chemical transformation of material incorporated from the surroundings, followed by deposition of the more permanent reaction-products within the growing system. It is well known how a crystal in a supersaturated solution increases in size while retaining definite form; the packing or mutual apposition of molecules similar in their shape and size and with their axes parallel explains the regularity in the structure of the whole resulting system; similarly an ice-crystal in subcooled water forms the center of deposition for further ice-crystals. In both of these cases material taken from the surroundings is transformed and deposited to build up a definite solid structure, but the transformation is physical rather than chemical. On the other hand in such examples of inorganic growth as the extension of a rust spot on a sheet of iron immersed in water, or the formation of "lead trees," the new material is formed by chemical transformation.

Inorganic growths dependent on such "germ-actions" often closely simulate organic forms; the frost patterns on window panes are a beautiful example; in this case the ice crystals are formed in apposition to one another and an apical growth results. The hexagonal crystal system of water is favorable to the formation of delicately branching arrangements; the characteristic "twinning," well seen in snow-flakes, also contributes to this result. The already formed crystal structure determines the formation of further crystalline deposit of the same kind, the apices or projecting angles of the structure forming the regions of most rapid deposition. In this manner long rows of crystal structure with lateral branches are built up by the opposition of new crystals at the extremities of the crystal-pattern already laid down. The resemblance to plant-growth depends on this peculiarity; a terminal or apical habit of growth is common to growing stems, leaves, roots and other plant organs, and determines the final structure of the whole system.

In the formation of tin-trees or lead-trees the form adopted by the growing system depends on a similar apical process of deposition, but in this case special electro-chemical factors enter. When a piece of zinc is placed in a solution of a lead salt, the zinc dissolves as Zn ions, and metallic lead separates out simultaneously; by continuation of this process there is built up by degrees a characteristic tree-like or branching structure. Each portion of lead as it is deposited forms a cathode in the zinc-lead couple; and hence more and more lead is separated from solution by a process of local electrolysis. The new metal is deposited in crystalline form and most rapidly at the apical regions, hence the deposit extends in a branching manner. A similar tendency to a branching

or arborescent form of deposit is not infrequent in the electrolytic separation of metals at cathodes.

Closer analogies to organic growths are seen in the precipitation-structures formed from metals immersed in solutions of salts whose anions form insoluble compounds with the metals; structures are built up of a tubular or quasi-cellular structure with semi-permeable membranes for walls; and the resemblance both in appearance and conditions of formation to certain types of plant growth is in many respects surprisingly close. These structures are related to those investigated by Leduc and Herrera, and formed by introducing crystals or solutions of alkali-earth and heavy metal salts into solutions which form precipitation-membranes with the introduced salt. The growths obtained by placing copper sulphate in ferrocyanide solutions are good examples. Leduc's book, "the Mechanism of Life," gives a fascinating account of these phenomena. The growths formed from metals are, however, peculiar in the fact that the structure-forming precipitate is deposited as the result of local electrolysis at the metallic surface; the presence of this electric factor thus renders these inorganic growths amenable to electric control (acceleration, retardation, directive influence), and this feature gives them an additional interest as models of organic growth-processes.

The methods of producing these growths are very simple. When a piece of iron wire is placed in a solution of potassium ferricyanide (2 to 4 per cent.), containing some egg-white or gelatine to act as protective colloid and a little sodium chloride, delicate blue-green vesicles and tubules of ferrous ferricyanide are quickly formed; the tubules grow out rapidly into the solution, and within half an hour or less the whole wire is covered with a dense filamentous growth resembling blue-green algae. Iron is an especially favorable metal for such experiments, apparently because of the presence of numerous local electric couples between different areas of the metallic surface, and filaments several centimeters long are readily obtained. These often exhibit delicate and regular cross-striations and other appearances suggestive of organic structure. If instead of iron the related metals, cobalt and nickel, are used, a different type of growth is obtained, coarser and more vesicular in structure and with finer tubules; many of the latter follow a characteristic tortuous or zig-zag course. To produce rapid growth with these metals it is necessary to accelerate the reaction by the contact of a nobler metal, *e. g.*, copper or platinum; a copper wire wound about one end of a strip of nickel (or cobalt) greatly promotes the growth of precipitation-structures. This effect, which

may be regarded as a kind of catalytic action, depends on the formation of a local couple, the nickel becoming anode and hence sending ions more rapidly into the solution; the accelerating influence of the copper is perceptible for some centimeters from the contact. Zinc and cadmium, another pair of closely related metals, also readily form highly characteristic vesicles and tubules, which frequently give rise to compound structures of quite remarkable beauty and symmetry, especially with zinc. Here also the contact of a nobler metal is necessary for rapid growth; the same effect may be produced by carbon, *e. g.*, by marking the strip of zinc with lead pencil. In all such experiments the growth is most rapid near the catalyzing metal or carbon, and a gradient in rate of growth is seen extending for several centimeters from the contact. Copper wires in contact with carbon or platinum also produce characteristic growths. Each metal in fact forms a definite type of precipitation-structure, having morphological characters which are specific for that metal; and it is interesting to note that the structures formed from closely related metals, *e. g.*, zinc and cadmium, or cobalt and nickel, resemble each other more closely in certain characteristic structural details (*e. g.*, the zig-zag tubules of cobalt and nickel) than when the chemical relationship is more distant. Something analogous to family resemblance is seen in such cases. In organisms also morphological similarity and chemical similarity are closely associated.

The resemblances between organic growths and precipitation-growths are of a general rather than particular kind, and too much emphasis should not be laid on superficial points of agreement. Yet when we consider the broad features of the transformative activity in the two cases and its fundamental determining and controlling conditions, certain identities appear which indicate that organic growth processes are largely conditioned by general factors of the same kind as those present in the above inorganic systems. In both cases the specific features of growth are referable to the specific peculiarities in the chemical composition of the structural material. We find that in the precipitation-growths a slight variation in chemical composition, *e. g.*, the substitution of cadmium for zinc, makes a definite change in the kind of structure developed; similarly it is possible that in organic growth a slight variation in the chemical composition of a structural protein, such as the substitution of one amino acid for another in the chain, may modify definitely the physical or other properties of the newly formed structure. One might suggest that the appearance of a sudden variation or mutation in an organism is the result of a chemical change of this kind. The formation of a new compound in forma-

tive metabolism may thus mean the appearance of a new structural and physiological character.[5]

But it is with respect to the problem of correlation, of the mutual influence exerted upon one another by growing parts of the same organism, that the metallic model shows perhaps its most striking resemblances to the growing and developing organism. We describe this phenomenon in organisms by saying, for example, that the growth of one region *inhibits* the growth of another, usually adjoining, region. Why it should do so is the problem. Why should a single blastomere of the 2-cell stage give rise to a half organism when the other blastomere develops by its side, but a whole organism when it develops in isolation? Or a plant bud begin growing only after an adjacent growing bud is removed or ceases active growth? Evidently some physiological influence of a repressive or inhibitory kind is exerted through a distance, and in at least some cases this influence can be shown to be independent of direct transfer of material between the two regions concerned. Such facts suggest that this type of control, like other forms of chemical control at a distance, may be electrical in nature. Is it possible that the bioelectric currents, always present in living organisms, influence the chemical processes underlying organic growth? Currents arising in association with the metabolic processes in a rapidly growing region might then control growth processes at a distance from this region, just as the electric currents in the iron-zinc-ferricyanide system control the formation of precipitation-tubules by one metal at a distance from the other.

The inhibiting influence exerted by an actively growing part of an organism upon the growth of adjacent parts is a phenomenon of too general occurrence to be referred to special conditions peculiar to any one organism or group of organisms. Its basis is apparently some physiological condition common to all organisms. The transport of growth-inhibiting substances is clearly not the condition in such well-known effects as the prevention of the growth of axillary buds in seedlings by the growth of the terminal bud. Recent experiments have shown that we can prevent the inhibitory influence from passing by conditions that do not interfere with the transport of material along the stem.[6] If the inhibitory influence is not due to transport, to what is it due?

5 If closely related species can be distinguished by precipitin or anaphylaxis tests, it is probable that mutants can similarly be distinguished from their parent organisms, although apparently no experiments of this kind have been tried. Leo Loeb finds evidence that there even exists a chemical differential between individuals of the same species (*cf. Amer. Naturalist,* 1920(Vol. 54, pp. 45, 55).

6 *Cf.* Child and Bellamy, *Science,* 1919, Vol. 50, p. 362; *Botan. Gazette,* 1920, Vol. 70, p. 249; E. N. Harvey, *Amer. Naturalist,* 1920, Vol. 54, p. 362.

We cannot answer this question fully at present, but it is perhaps sufficient to point out that the fundamental problem involved is the general problem of the transmission of physiological influence in living protoplasm. Through what means does a physiological process occurring at one region affect processes at other regions? If we leave out of consideration the numerous instances where the mechanism of physiological correlation is evidently of a transportative kind, as seen in the effects of the various growth-determining hormones (thyroid, pituitary, ovary, etc.,) or of the hormones determining glandular secretion or rate of respiration, we have remaining a large class of effects highly characteristic of living matter in all of its forms, namely, those transmissions of local states of activity or excitation known generally as protoplasmic transmissions. Sherrington points out that in higher animals there exist two chief methods by which the various chemical and physiological activities are integrated or made to work in harmony, namely (1) integration by transport of chemical substances (usually special metabolic products) from region to region, chiefly in the blood stream, and (2) integration by transmission of physiological influence, excitatory and inhibitory, to a distance through the living protoplasm without material transport between the regions; the chief example of this type of process is nervous transmission. The nervous system is the chief integrating and coordinating system in higher animals; nervous transmission, however, is merely a specialized form of a type of transmission present everywhere in protoplasm. If the metabolic processes underlying (*e. g.*) muscular contraction can be thus controlled at a distance, it is not difficult to believe that those underlying growth can be similarly controlled. This mode of influence has been called physiological distance-action, after the analogy of chemical distance-action, and our problem is to determine its physico-chemical nature. One of its most characteristic manifestations is seen in the transmission of growth-inhibiting and other formative and correlating influence in growing and developing organisms.

For our purpose the most instructive instances are those in which the growth of one region controls that of an adjoining region. How can a growing bud on a piece of stem in a Bryophyllum prevent the growth of roots or shoots on an attached leaf,[7] or one growing axis inhibit another in the blastodisc of a Fundulus egg,[8] unless there is transfer of inhibiting substances from the actively growing to the inhibited area? or unless the actively growing region appropriates all of the available nutriment? Yet both of

[7] J. Loeb, *Botan. Gazette*, 1915, Vol. 60, p. 253.

[8] C. R. Stockard, *Amer. Journ. Anatomy*, 1921, Vol. 28, p. 115.

these modes of explanation are apparently inapplicable in many cases. The only general physical conception which seems to me to throw some light on this and related problems is the one which regards physiological distance-action as a special case of the phenomenon called by Ostwald "chemical distance-action," and well known to all students of electrochemistry. By this term is meant the influence which the chemical reaction at one electrode-area of a circuit exerts upon those at the other electrode-area. This influence has a reciprocal character, dependent ultimately on the fact that the flow of electricity around the circuit is in one direction; hence oxidation at one electrode is associated with the reverse process, reduction, at the other. According to Faraday's law the rates of the two opposite electrochemical reactions must be equal, hence variation in the one involves a corresponding variation in the other. The above precipitation-growths from metals furnish many striking examples of this influence; the contact of a piece of zinc with an iron wire immersed in a ferricyanide solution prevents the outgrowth of precipitation-filaments from the iron, even at a distance of several centimeters from the contact; at the same time their formation from the zinc is promoted. In this case it is not possible to assume that inhibitory substances are derived from the zinc, where growth of filaments is rapid, and transported to the iron. Yet there is a definite influence, exerted through a distance, which inhibits the outgrowth of precipitation-filaments from the iron so long as they are being rapidly formed from the zinc. This influence is electrical and depends simply on the passage of the electric current around the circuit constituted by the two metals and the salt solution. Metallic zinc in contact with the solution is electrically negative or anodic; the zinc ions given off to the solution form the precipitate of zinc ferricyanide which builds up the filaments. The iron is cathodic, *i. e.*, the positive current is in the direction from solution to metal, thus preventing the passage of iron ions into solution; hence no precipitate forms. If, however, we sever the iron wire from metallic connection with the zinc, *e. g.*, by cutting off its projecting extremity, the isolated portion at once develops filaments. The compensating or inhibiting condition is removed when the electrical circuit between the two metals is broken.

In cases of regeneration in animals or plants the removal of a portion of the organism frequently initiates an extensive process of growth and development at the cut surface. We may infer therefore that many stationary or quiescent regions of the organism are capable of active growth or proliferation, but do not manifest this power until they are removed from the influence of other

regions. Is it possible that in such cases what prevents growth is the passage of electric currents between regions of different growth-activity, the more active regions—which are those of greater metabolic or synthetic activity—inhibiting the less active through the currents associated with their growth?

There are many facts which point in this direction. Hermann and Müller-Hettlingen found that in seedlings the regions near the actively growing zones—terminal buds or root-tips—were negative relatively to those near the cotyledons;[9] regenerating hydranth heads are negative to the stems;[10] the growing zones in planarians and annelids are negative to intermediate regions.[11] Further studies in this field are desirable, but all of the evidence now available agrees in indicating that regions where growth and cell-division are active are in general negative to inactive regions—negative, that is, in the same sense as the stimulated region of a muscle or nerve is negative to the unstimulated. The regions where the positive stream of the bioelectric circuit enters the living system from the surrounding medium are the regions of most active growth; those where it leaves are the quiescent or less active regions. The physiological or metabolic asymmetry is associated with an electrical assymmetry or potential difference. Such actively growing regions, in addition to their electro-negativity, show in general a higher oxygen-consumption and carbon-dioxide output and a greater susceptibility to poisons than less active regions. A connection between the metabolic processes underlying growth and the bioelectric currents is thus indicated. In plants removal of oxygen has been shown to abolish these currents, a fact indicating that oxidation-processes are concerned in their production.

If the bioelectric currents have a direct influence on growth, we should expect that electric currents led into the growing systems from outside sources would have a similar influence. Regions where the positive stream enters the growing system from the surroundings should be favorably influenced in their growth, since such regions correspond to the "negative" regions in the bioelectric circuits of growing organisms; these regions, as just shown, are those of most rapid growth. Recently it has been found by Lund that regeneration of new polyps from the cut stems of the hydroid Obelia may be experimentally controlled by weak electric currents passing lengthwise through the stem; the formation of hydranths is promoted where the current passes so as to enter the stem, *i. e.*, at the cut end facing the anode, and inhibited at the

9 *Pflüger's Archiv.*, 1883, Vol. 31, p. 193.

10 A. P. Mathews, *Amer. Journ. Physiol.*, 1903, Vol. 8, p. 294.

11 *Cf.* C. M. Child, *Biol. Bulletin*, 1921, Vol. 41, p. 90.

other end. A polar influence on formative processes, corresponding to that on stimulation processes, is thus shown.[12] These interesting observations agree with those of the Indian investigator, Bose, who finds that the electric current influences growth-movements in higher plants in a polar manner, the anode enhancing and the cathode depressing the normal rate;[13] and also with the recent experiments of Sven Ingvar in the Yale laboratory, which have shown that weak constant currents exert a directive influence on the outgrowth of the processes from embryonic nerve cells; here also a polar influence is seen, the processes growing toward the anode being morphologically different from those growing toward the cathode.[14]

If the growth processes in living organisms are thus subject to artificial electrical control, it seems reasonable to infer that the natural or physiological methods of control in normal growth and development are also in large part electrical. The bioelectric currents would thus become essential formative factors, just as they are essential factors in excitation and transmission; organic polarity, as Mathews suggested, would become electrical polarity. This, however, would again be referred to chemical polarity, since we must assume that the bioelectric currents, like the currents in metallic couples or other current-yielding systems (where the energy of the current is derived from chemical reactions at surfaces) are the expression or accompaniment of chemical processes in the living system. The metabolic processes underlying growth are of complex and largely unanalyzed nature, but we know that they are typically associated with the consumption of oxygen and include specific syntheses by which the new structure-forming compounds are built up. Can we then say that the chief method of construction of such compounds is electro-synthesis? Such a characterization may not in itself add much to our knowledge, but it suggests directions in which research may be profitable. It implies, especially, that the basis of all such effects, like the basis of other manifestations of irritability, is to be sought in the conditions determining the electrical sensitivity of living matter, one of its most fundamental characteristics. This in turn is almost certainly conditioned by the polyphasic and film-pervaded structure of the protoplasmic system.[15]

[12] E. J. Lund, *Journ. Exper. Zoology,* 1921, Vol. 34, p. 471.

[13] J. C. Bose, *Proc. Roy. Soc.,* B. 1918, Vol. 90, p. 364

[14] S. Ingvar, *Proc. Soc. Exper. Biol. and Medicine,* N. Y., 1920, Vol. 17, p. 198.

[15] *Cf.* my discussion of the basis of protoplasmic irritability and transmission in THE SCIENTIFIC MONTHLY, 1919, Vol. 8, pp. 457 and 552.